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Previews

Renaissance of MMPs as Therapeutic Targets? Maybe

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Matrix metalloproteases (MMPs) have been implicated in a number of different human diseases and are currently one of the actively pursued targets in drug discovery and development. In this issue of *Structure*, Udi and colleagues describe how an inhibitory antibody, LEM-2/15, affects a member of the MMP family, MT1-MMP.

Matrix metalloproteases (MMPs) play a pivotal role in tissue remodeling by virtue of their unique ability to degrade macromolecules of extracellular matrix (ECM). The activity of these enzymes is inexorably linked to the control of ECM restructuring during morphogenesis, tissue repair, angiogenesis, uterine involution, and bone resorption. MMPs have been implicated in various pathological conditions including arthritis and inflammatory diseases. Malignant cells exploit MMPs to promote tumor invasion and metastasis. Hence, in the recent past, MMPs were considered to be rich targets for drug development. Understandably, a great deal of effort was devoted to produce small molecule inhibitors targeting the active site (Hopkins and Groom, 2002). However, development of effective therapeutics based on this strategy remains an elusive goal to a large extent because of the high structural homology at the active site shared by proteases of this family (Hopkins and Groom, 2002, Overall and López-Otín, 2002; Sela-Passwell et al., 2010a). Moreover, the first generation of MMP inhibitors failed in clinical trials because of unspecific inhibition of other processes that the MMPs are involved in in vivo (López-Otín et al., 2009; Overall and Kleifeld, 2006). Targeting specific inhibitory sites residing outside the conserved catalytic cleft was suggested as an alternative drug design approach to control MMPs' activity in vivo (Sela-Passwell et al., 2010b). Recently, the pursuit of selective MMP inhibitors has begun to shift toward selecting monoclonal antibodies targeting exosites and allosteric interactions of the specific enzymes.

Thus far, several inhibiting antibodies against MMPs have been reported in the literature. However, information regarding the inhibition mechanism is still somewhat limited. For example, REGA-3G12, a highly selective MMP-9 inhibitor that binds with high affinity (Hu et al., 2004; Martens et al., 2007) recognizes the N-terminal part of the catalytic domain of MMP-9 and does not bind the catalytic zinc ion (Martens et al., 2007). Moreover, Dyax recently developed a potent and highly selective membrane type 1 (MT1)-MMP antibody, DX-2400 (Devy et al., 2009). This antibody inhibits MT1-MMP in a competitive manner, implying direct interaction with the zinc ion or blockage of the catalytic cleft. In addition, another anti-MT1-MMP antibody, termed 9E8, has been reported recently (Ingvarsen et al., 2013; Shiryaev et al., 2013). This antibody inhibits an MT1-MMP dependent MMP-2 activation while maintaining other functions, and yet the molecular details remain to be clarified. Intriguingly, Sela-Passwell et al. (2012) recently reported an antibody that inhibits the catalytic activity of MMP-2/9 by direct interaction with the catalytic zinc ion. These reports suggest that the mechanisms by which antibodies can inhibit proteases include either direct binding at the catalytic cleft or indirect inhibition by binding to allosteric regions.

In this issue of *Structure*, Udi et al. (2015) present a detailed molecular and biophysical description of the interaction between MT1-MMP with an inhibitory antibody, LEM-2/15. This antibody was generated against an exposed surface loop of MT1-MMP (residues 218–233, the V-B loop) (Gálvez et al., 2001). Kinetic and binding studies confirmed that LEM-2/15 is a highly selective potent MT1-MMP inhibitor, affecting mainly the collagenolytic activity of MT1-MMP in biological assays. LEM-2/15 inhibits the enzymatic activity of MT1-MMP against a small synthetic peptide as well as against native substrates, collagen type I, and gelatin.

Here, protein crystallography sheds light on the molecular mechanism of the allosteric inhibition of MT1-MMP. Interaction of the enzyme with LEM-2/15 induces conformational changes so that the V-B loop of MT1-MMP

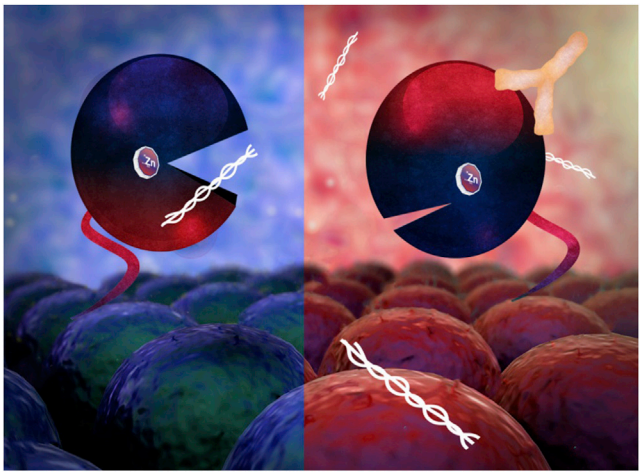

Figure 1. Binding of LEM-2/15 Antibody to MT1-MMP Induces Conformational Perturbation, Leading to Narrowing of the Substrate Binding Cleft
(Left) MT1-MMP is shown residing attached to the cell surface and engaged with the substrate. (Right) Binding of LEM-2/15 antibody to the allosteric site inhibits substrate binding and thus the activity of MT1-MMP.

"flips out" toward the antibody, resulting in narrowing of the substrate-binding cleft (Figure 1). The narrowing of the substrate binding cleft between the V-B loop and the region of the active site involved in substrate binding, S1', along with likely imposed constrains on the loop flexibility explain the basis of the allosteric inhibition by the LEM-2/15 antibody.

Most impressive is the fact that the antibody reduced cell surface collagenolytic activity in a fibrosarcoma cell line having little effect on the enzyme dimerization or on MT1-MMP-dependent activation of MMP-2. This work marks the progress toward identification of the enzyme specific surface exposed epitopes that are important for the control of enzymatic activity and can provide an entree into development of novel therapeutics

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It Takes Two to Rule Translation Elongation

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In this issue of *Structure*, Glatt and colleagues report the structure of the Kti11/Kti13 heterodimer. This study reveals how dimerization and Fe^{2+} binding are required for modification of both tRNA and EF2, thus suggesting a mechanism for regulation of translation elongation via two different pathways.

The amount of proteins synthesized in a cell must be tuned in response to changing environmental and developmental conditions. While regulation of gene expression at the transcriptional level has been described for decades, the importance of translational control in cellular responses has more recently also been recognized, and an increasing number of subtle mechanisms to regulate translation elongation have been discovered.

Translation elongation factor 2 (EF2) occupies an essential role in protein translation, where it catalyzes the translocation of the ribosome along the mRNA. EF2 contains a diphtamide modification on a conserved histidine residue, which interacts with the ribosomal decoding center (Schaffrath et al., 2014). In eukaryotes, addition of this modification occurs via a four-step pathway involving the proteins Dph1–Dph7. The first step in this pathway is catalyzed by the [4Fe-4S] cluster-containing heterodimeric protein complex Dph1/Dph2, with the help of Dph3 and Dph4. Although the diphtamide group of EF2 is the target for ADP-ribosylation by the bacterial diphtheria toxin, its exact physiological role is not yet fully understood. Recently, it has been suggested that cells have an in-built capacity to ADP-ribosylate the diphtamide group and that this activity is increased under certain cellular stresses, leading to a global decrease of protein translation at the expense of an upregulation of IRES-dependent translation of mRNAs implicated in oxidative stress protection (Argüelles et al., 2014) (Figure 1).

Codon bias in certain subsets of genes, coupled to regulation of specific tRNA modifications, forms another strategy to regulate translation elongation. Chemical modifications at the wobble position of tRNA play an important role in translation rate and accuracy by stabilizing codon-anticodon interactions in the A site of the ribosome. Accordingly, it has become increasingly apparent recently that tRNA wobble